Risk factors associated with the development of active tuberculosis among patients with advanced chronic kidney disease

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Renal failure and active tuberculosis in a high incidence UK city

Running title: Renal failure and TB in a high incidence city

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Highlights (3-5 bullet points, 85 char per point)

- Those with advanced kidney disease or receiving dialysis are at high risk of active TB
- Cases occurred steadily over the period observed, regardless of time on dialysis
- Those of Asian/Asian British or black/black British ethnicity were at highest risk
- Testing and treating for latent TB is justified in high risk groups receiving or approaching dialysis

Keywords

- Tuberculosis, epidemiology
- Latent tuberculosis
- Renal Insufficiency, Chronic
- Renal dialysis

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Abstract (229 words)

Objectives: The risk of developing active TB is greater in those receiving haemodialysis. This study aimed to describe the incidence of active tuberculosis among patients referred for management of kidney disease and dialysis in a high incidence UK city, with the purpose of informing latent TB testing and treatment practice.

Methods: Information from the tuberculosis register was cross-referenced with the Department of Renal Medicine patient information system. All patients seen between 1st January 2005 and 1st October 2016 were included in the analyses with the exception of those with prior TB.

Results: 68 cases of active TB were identified, an incidence of 126/100,000 patient-years (95% CI 97-169). Incidence was lowest in those with CKD 1 or 2 and rose as high as 256/100,000 patient-years (95% CI 183-374) in those receiving renal replacement therapy. 48% of cases were pulmonary and 87% of TB patients gave their ethnicity as either black/black British or Asian/Asian British, significantly more than in the non-TB renal group. Cases occurred steadily over the time period in which patients were in the cohort.

Conclusion: TB incidence was very high among those receiving renal replacement therapy or CKD 4 or 5. Most cases occurred in those of an Asian/Asian British or black/black British background. Testing and treating such patients for latent TB is justified and should include those who have been receiving renal replacement therapy for some years.

Introduction

It is estimated that around one quarter of the world's population is infected with tuberculosis (TB) (1). Over a lifetime a healthy individual with latent TB has 10-15% chance of developing active TB infection. This risk is greatly increased in those with certain forms of immunosuppression or co-morbidity. For example, it doubles or trebles in those receiving TNF-antagonists for treatment of conditions such as rheumatoid arthritis and psoriasis(2). This has led the UK Medicine and Healthcare Regulatory Agency to recommend that all patients in whom treatment with TNF-antagonists is being considered are first screened for latent TB and treated if necessary(3).

Patients receiving haemodialysis are known to be at increased risk of latent TB reactivation(4). Some studies estimate this as great as 25 times that of an otherwise healthy individual(5). Even patients experiencing acute kidney injury and requiring short spells of dialysis(6) or those with chronic kidney disease (CKD) not yet requiring it have been shown to have higher rates of incident active TB(7). There is at present little consensus on whether to screen dialysis patients for latent TB routinely. Current UK advice recommends against the practice suggesting instead that those at high risk should be considered on a case-by-case basis(8) whereas more recent guidance from the World Health Organization recommends testing for all patients receiving dialysis(9).

Birmingham is the UK's second city. 24% of its population was born overseas, mostly in India and Pakistan (Office for National Statistics 2011). It has a TB incidence of 29 per 100,000/year, one of the highest outside of London, with approximately 350 active cases treated each year, 75% of whom were born overseas. This compares with a rate of 10.2 per 100,000/year in 2017 in England (10). Heart of England NHS Foundation Trust provides renal care and dialysis services to the population of East Birmingham and Solihull. In line with national guidance it does not routinely screen for latent TB. This study aimed to describe the incidence of active TB within patients referred for management of kidney

disease and dialysis with the purpose of informing the unit's latent TB testing and treatment practice.

Methods

The Heart of England NHS Foundation Trust TB register was cross-referenced with the Department of Renal Medicine patient information system. This holds basic information on all patients referred to the renal department with kidney disease, as well as those receiving peritoneal or haemodialysis. All patients seen between 1st January 2005 and 1st October 2016 were included in the analyses with the exception of those with prior TB. Patients were considered to have come under the care of the renal unit on the earlier of the date of their first estimated glomerular filtration rate (eGFR) record or their first entry in their electronic patient record. Eligible renal unit patients were followed up until the earliest of the following dates: patient diagnosed with TB (incident case), patient death, patient transferred out of renal unit, and 1st October 2016. CKD stage was taken from a single eGFR result or evidence of dialysis. Patient follow-up was split by CKD stage and dialysis status (pre/post). All analyses were carried out using Stata 14.2.

Ethics

As a service improvement project using data already available to us in the course of routine clinical care, ethical approval was not required.

Results

Demographics

There were 8767 patients within the renal cohort representing 53,833 patient years. The median age at entry was 66 years (mean 62 years). 71% were white, 18% Asian/Asian British and 5% black/black British. 56% were male. By the end of follow-up 24% of the cohort was at CKD 3 or less, 45% were at CKD 4 and not receiving renal replacement therapy, with 31% of the cohort receiving some form of renal replacement therapy.

Cases of active tuberculosis

68 patients developed tuberculosis during the time period studied. Those developing TB were younger at entry to the renal cohort (mean age 55 versus 62.5, p<0.001) and had higher death rates (23.5% vs 37%, p=0.022) than those who did not develop TB. They were also significantly more likely to identify as Asian/Asian British or black/black British (p<0.001) and to have received intravenous iron therapy (33.8% vs 20.3%, p=0.006). There was no statistically significant association with being diabetic (table 1). Most patients had no identifiable additional immunosuppression with 11 being on immunosuppression drugs for their primary disease and 2 with diagnoses of HIV.

Of the 68 cases there were 11 instances of intrathoracic lymph node disease and 33 pulmonary cases. 22 patients were smear positive, of which 86% were culture positive. Just 1 of the 31 smear negative sputum specimens was culture positive. Among the 23 culture positive specimens one was resistant to isoniazid alone, and one was multi-drug resistant (to rifampicin and isoniazid).

8 of the 16 recorded deaths among TB patients occurred within 2 years of starting TB treatment. 2 deaths were directly attributable to TB, 1 had no information available and the remaining were due to unrelated respiratory or cardiovascular disease.

Molecular epidemiology of active TB cases

MIRU-VNTR genotyping was available for 20 of the 23 culture positive specimens. For the nine specimens prior to 2010, this was 15-locus, and later, 24 locus. In addition 12 of these had had whole genome sequencing (WGS) performed as part of a separate study. Whilst MIRU-VNTR suggested that 3 patient pairs might have had related TB infections this was not supported by single nucleotide polymorphism typing from WGS. 1 patient without WGS data available had a similar MIRU-VNTR type to one other but no epidemiological links were identified during contact tracing. 4 of the 20 cases were identified by WGS as part of separate larger UK tuberculosis clusters.

Incidence of active tuberculosis

The overall incidence of TB within the renal cohort was 126/100,000 patient-years (95% CI 97-169). It was as low as 92/100,000 (95% CI 49-191) in those with CKD 1 or 2 and as high as 257/100,000 patient years (95% CI 183-374) in those receiving renal replacement (figure 1). There was no specific time point at which TB cases were more likely to occur, with cases occurring steadily over the time individuals spent in the cohort (figure 2). TB incidence was significantly higher in those patients who received intravenous iron therapy compared to those who did not (table 1).

Discussion

It is recognized that those patients with advanced kidney disease or undergoing renal replacement therapy are at high risk of developing active TB(4). Over the approximately 10 years of data in our study we identified 68 cases of active TB, equating to an overall incidence of 126/100,000 patient-years in the cohort (95% CI 97-169). Whilst not directly comparable, Public Health England reports an overall rate of 29/100,000 people per year for the City of Birmingham. Incidence was lowest in those with CKD 1 or 2 and rose as high as 256/100,000 patient-years (95% CI 183-374) in those receiving renal replacement therapy. We also noted a significant association with the receipt of intravenous iron therapy. Iron is a co-factor supporting mycobacterial growth(11) and whilst it is theoretically possible there is a direct link between iron use and the emergence of active tuberculosis, use of iron may simply be associated with more significant renal disease and debilitation.

Patients developing active TB did so gradually over their time in the study cohort. There was no apparent point of increased risk, for example around the time of starting dialysis. This would suggest that there is benefit in testing those who are already long established on renal replacement therapy when launching a new testing programme.

48% of cases were pulmonary and each of these cases prompted lengthy and expensive contact tracing exercises. Whilst there were no reported cases of TB

transmission, dialysis units are potentially high-risk environments, gathering together immunodeficient individuals for several hours each week. Transmission has been reported elsewhere(12) and each active case on a dialysis unit results in large and expensive screening exercises. These could well be avoided if patients with latent TB were identified and treated on entering dialysis programmes.

Guidance regarding testing for latent TB in this population varies, recognizing the differences in incidence between patient groups or geographical areas (1,6) and the limitations of current diagnostics in this context. 87% of TB patients in our cohort gave their ethnicity as either black/black British or Asian/Asian British, significantly more than in the non-TB renal group. Latent TB testing would be employed most cost-effectively in these groups. Our population did not include a significant numbers of Caucasians from countries with a high TB incidence. Where costs are a constraint it would be appropriate to focus testing and treating those of an ethnicity, or country of origin, associated with a high risk of incident TB. In addition whilst the apparent association with iron administration cannot be assumed to be causal the need for its use certainly indicates a patient group at risk of TB. Testing should be considered in all patients with advanced renal failure regardless of the need for renal replacement therapy.

The method by which a diagnosis of latent TB is made in this population is not straightforward. The sensitivity of tuberculin skin testing is reduced – as is to a lesser extent that of the interferon-gamma release assay (IGRA)(13) – in those receiving dialysis. In the general population T-spot and Quantiferon (QFT) have a sensitivity of between 68-90% and 52-70% respectively with a specificity of 97% for both(14,15). In comparison a meta-analysis of studies examining latent TB diagnosis in dialysis patients gave a pooled sensitivity of around 50% and specificity of 65% for both tests in the dialysis population(16,17) – with TSTs giving a pooled sensitivity of 31%. The low sensitivity of IGRAs must be understood in the context of the lack of gold standard for the diagnosis of latent TB. The studies from which these figures were derived varied in how they

defined latent TB, using one or a combination of history of treated TB, history of TB contact, and radiological evidence of past TB. The sensitivity of QFT is as high as 71% if measured against the more liberal standard of any one, or multiple, of those risk factors. It is clear that IGRAs are not a rule-out test for latent TB. A negative test in a patient highly likely to have been exposed to TB – for example with chest X-ray changes consistent with past TB infection or recent confirmed TB contact – may still benefit from treatment and a clinical assessment of TB risk is indicated. Treatment is not without its risks and such patients are likely to be best managed on a case-by-case basis by those with experience in tuberculosis. If not treated they should be encouraged to report the subsequent development of TB symptoms promptly.

Beyond sensitivity and specificity there are practical issues with IGRA result interpretation. Firstly results may be reported as "indeterminate" due to either a high background level of interferon-gamma activity within the negative control or low response to the positive control(18). T-spot produces fewer indeterminate results than QFT (4.8% vs 12.6%) among dialysis patients(16) which may favour its use in this patient group. Secondly, serial IGRA tests among renal patients over time demonstrates a variable level of conversion and reversion unrelated to treatment for latent TB(19). A stronger initial response is associated with sustained positivity and may have a role in deciding who should be treated(20). Sensitivity can be improved by a repeat testing protocol. In one small study those patients with 2 or more positive IGRAs conducted over a short time period were more likely to develop active TB over the follow-up period(21).

There were a number of limitations to this study. It was retrospective and certain assumptions had to be made with respect to the data. Patients were assigned to a CKD stage by a single eGFR result and some may have been misclassified. The assumptions made in defining the observation period may have led to time overestimates if patients were not resident in the Birmingham and Solihull region for the entire period. TB cases diagnosed in another district would not have been included as incident TB cases which may have led to an underestimate of true TB incidence. Finally this study has reported a single

incidence derived from a 10-year period. Over this time TB rates have fluctuated from an English peak of 15.6/100,000/year in 2011 before declining to current levels.

In conclusion our data indicates that testing and treating for latent TB is justified in dialysis recipients of an ethnicity or country of origin associated with a high risk of incident TB even if well-established on dialysis. It should also be considered in all patients with advanced renal failure regardless of the need for renal replacement therapy – particularly those requiring intravenous iron. It is less clear whether there is a benefit in testing and treating lower risk patients. Our approach to the use of immunosuppressive biological therapies would suggest they should be but the number needed to test and treat in order to prevent a case of active TB is not known. Current WHO guidance is supportive of universal testing of dialysis recipients(9).

IGRAs are preferred over TST for reasons of sensitivity with T-spot likely to be most useful in clinical practice due to its lower rate of indeterminate results. There is insufficient evidence to suggest a serial testing strategy at present but it may have a role in the management of those patients who are reluctant to take treatment on the basis of a single result, or in whom treatment would be potentially complex. The relatively low sensitivity of IGRAs must be considered and testing should be combined with a thorough clinical risk assessment. The prospective validation of a combined IGRA and clinical risk assessment protocol is an important area for future research. Those at high risk of latent TB with negative tests – or positive tests electing not to take treatment – should be discussed with a specialist and encouraged to report the later development of any symptoms suspicious for TB.

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Table 1: Comparison of renal cohort patients, with and without incident TB

	Incident TB	No incident TB	significance*
Renal patients (%)	68 (0.8%)	8699 (99.2%)	
Mean age at entry (SD)	55.0 (16.0)	62.5 (18.7)	p<0.001
Median age at entry (IQR)	55.1 (39.6-69.1)	67.0 (50.4-77.0)	
Mean age at exit (SD)	60.2 (17.2)	66.3 (18.0)	p=0.003
Median age at exit (IQR)	60.0 (46.6-75.0)	70.4 (54.6-80.3)	
Male (%)	36 (53%)	4883 (56%)	p=0.597
Ethnicity (%)			
White	7 (10.3%)	6260 (72.0%)	
Asian/Asian British	53 (77.9%)	1556 (17.9%)	
Black/Black British	7 (10.3%)	446 (5.1%)	
Other Ethnic Groups	0 (0.0%)	64 (0.7%)	
Mixed	0 (0.0%)	51 (0.6%)	
Unknown	1 (1.5%)	322 (3.7%)	p<0.001
Mean follow-up time in renal unit in years (SD)	10.2 (4.6)	8.3 (6.2)	p=0.001
Median follow-up time in renal unit in years (IQR)	10.6 (7.7-13.2)	7.9 (2.8-12.2)	
Deaths (%)	16 (23.5%)	3218 (37.0)	p=0.022
Mean age at death in years (SD)	67.4 (16.1)	74.9 (12.7)	p=0.003
Mean age at death in years (SD)	71.7 (53.1-80.9)	77.6 (68.5-83.9)	
CKD stage at exit (%)			
1 or 2	8 (11.8%)	717 (8.3%)	
3	11 (16.2%)	1368 (15.8%)	
4+ pre-dialysis	22 (32.4%)	3903 (44.9%)	
4+ post-dialysis	27 (39.7%)	2711 (31.2%)	p=0.175
IV iron treatment (%)	23 (33.8%)	1764 (20.3%)	p=0.006
Mean dialysis duration in years since entry to renal unit (SD)	6.3 (3.6)	6.0 (6.8)	p=0.050
Median dialysis duration in years since entry to renal unit (IQR)	6.6 (3.6-8.3)	3.8 (1.2-8.3)	
Diabetes at exit (%)	23 (33.8%)	2237 (25.7%)	p=0.128

* Chi-square test for count data; Wilcoxon rank-sum test for continuous data

Table 2
TB cases: clinical and microbiological features

	Number
TB site	
Pulmonary	33
Pleural	1
Abdominal	3
Intrathoracic LN	11
Extrathoracic LN	1
Miliary	4
Spinal	3
Other (joint, pericardial, urinary, unknown)	12
Diagnostics	
Smear positive (n culture positive)	22 (19)
Smear negative (n culture positive)	31 (1)
Histology (n culture positive)	8 (3)
Drug sensitivity (from 23 culture positive)	
Fully sensitive	21
INH mono-resistant	1
RIF resistant or MDR	1
Treatment duration	
6 months	40
7-9 months	7
10-12 months	9
13-24 months	3
Not treated	1
Unknown	7
Immunosuppression	
None	52
Immunosuppressive drugs	11
HIV	2
Not known	3
Renal diagnosis	
Diabetes	15
Glomerulonephritis	8
Hypertension	16
HIV nephropathy	1
Other	14
Unknown	14

Figure 1
TB incidence among renal patients in East Birmingham, UK.
Y-axis: cases/100,000 person years (95% confidence intervals)

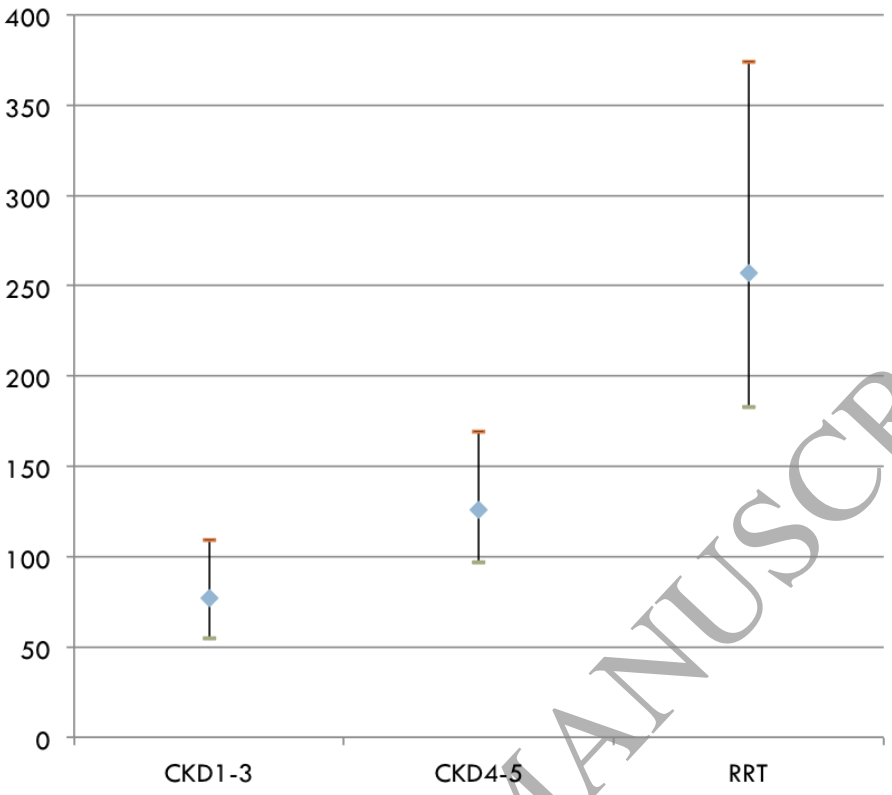
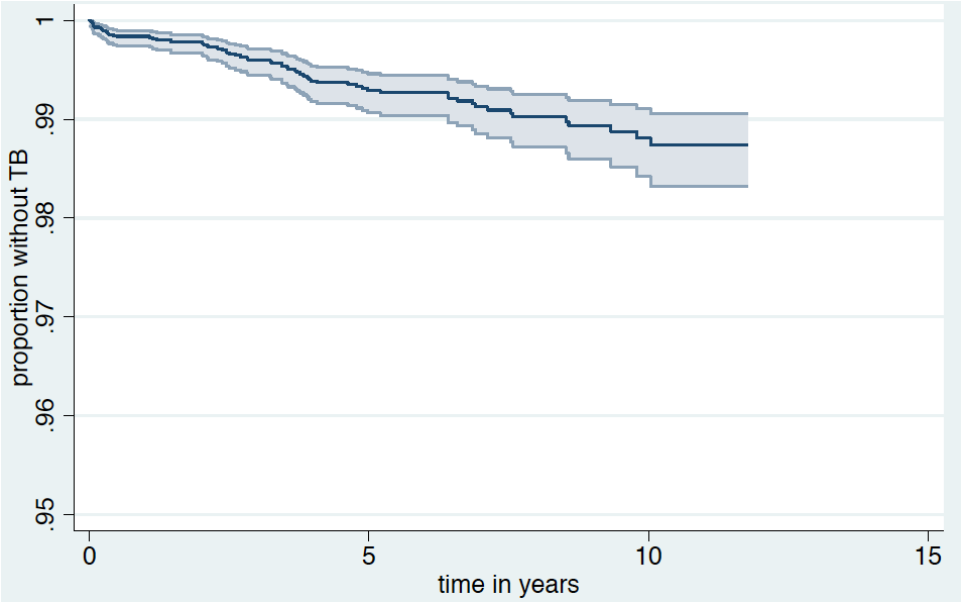


Figure 2: TB-free survival among renal cohort patients with CKD 4/5 or receiving renal replacement therapy.



Time starts from earliest of CKD 4/5, dialysis or first seen in clinic with CKD 4/5/dialysis